TGFb+MMP+iIn b Sequence

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ATGCCGCCT	CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC	GCIGCIGCCG	1234367890	1234567890	1234567890	
MetProProS	erGlyleuAr	gleuleuPro		TIPLICATION OF THE	GCPACIGNIG	60
		gocurcuito	beateatear	Toteuteuri	breareavar	
CIGACGCCIG		. OGCOGGACTA	TCCACCTGCA	AGACTATOGA	CATCCACCITAC	120
LeuThrProG	lyProProAl	aAlaGlyLeu	SerThrCysL	ysThrIleAs	pMetGluLeu	120
GIGAAGCGGA	AGCGCATCGA	GGCCATCCGC	GGC AGATIC	יייבע עייבודניי		700
ValLysArgL	ysArgIleG1	uAlaIleArg	GlyGlnIleL	euSerivsie.	ngarione a	180
ACCCCCCCA	GCCAGGGGGA	GCTGCCCCCC	GGCCCGCTGC	CCCACCCCT	GCICGCCCIG	240
SerProProS	erGlnGlyG1	uValProPro	GlyProLeuP	roGluAlaVa	lleuAlaLeu	
		•				
TVrAsnSerT	pramaca	OGIOCOCCG	GAGAGIGCAG	AACCGCAGCC	CCACCCICAG	300
-1	inurgushur	gValAlaGly	GluserAlaG	luProGluPr	oGluProGlu	
GCCGACTACT	ACGCCAAGGA	GGTCACCCCC	CHATTEN CHES	עיירטעעענינוו	CNACCIANAMO	250
AlaAspTyrT	yrAlaLysGl	uValThrArg	ValleuMetV	alGluThrHi	SASTCIUTIO	360
				•		
TATGACAAGT	TCAAGCAGAG	TACACACAGC	ATATATATGT	TCTTCAACAC	ATCAGAGCTC	420
TYTASPLYSP	heLysGlnSe	rThrHisSer	IleTyrMetP	hePheAsnTh	rSerGluLeu	
AroGluAlaV	alProGluPr	OGIGITOCIC oValleuleu	TOUGGCAG	AGCIGCGICT	GCTGAGGAGG	480
		ovaniemen	Servidariac	Tuleuargle	uLeuArgArg	
CICAAGITAA	AAGTOGAGCA	GCACGTOGAG	CIGTACCAGA	AATTACTACTAA	בינוניירוניינעעי	540
LeuLysLeuL	ysValGluGl	nHisValGlu	LeuTyrGlnL	ysTyrSerAs	nAsnSerTro	J 40
AMTERICA	CCAACCGCT	GCTGGCACCC	AGCGACTCGC	CAGAGIGGIT	ATCTTTTGAT	600
.ugiyile05	erasiargle	uLeuAlaPro	SerAspSerP	roGluTrpLe	uSerPheAsp	
GTCACOGGAG	TIGIGGGA	GTGGTTGAGC	Comeración	3 3 3 TTTY 3 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	~~~~	
ValThrGlyV	alValArqGl	nTrpLeuSer	AmGlyGlyG	Juliacing.	CITIOGCIT	660
AGCGCCCACT	GCTCCTGTGA	CAGCAGGGAT	AACACACTGC	AAGTGGACAT	CAACGGGTTC	720
SerAlaHisC	ysSerCysAs	pSerArgAsp	AsnThrLeuG	lnValAspI1	eAsnGlyPhe	
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ThrThrGlvA	mamclude.	CCTGGCCACC	ATTCATGGCA	TGAACCGGCC	TITICCICCIT	780
	raurgeryns	pLeuAlaThr	TIGHTSTAM	etAsnArgPr	oPheLeuLeu	
CTCATGGCCA	CCCCCCTCGA	GAGGGCCCAG	CATTTTCAAA	COCCENTRACIO	dramma)	040
LeuMetAlaT	hrProLeuG1	uArgAlaGln	HisLeuGlnS	erGluPheGl	vGlvGlvGlv	840
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Corport	CCTTTCCCC	CCCACCCCCC	TCZCCCCCC	CAATCAACTA	TAAGCAGCIC	900
SCILIOIGIG	TATELLIMAT	aGlyGlyGly	SerAlaAlaA	laIleAsmTy	rLysGlnLeu	
GlnLeuGlnG	luAroThrAs	CATTOGGAAA nileArgLys	TGTCAGGAGC	'ICCTGGAGCA	OCTGAATGGA	960
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TGFb+MMP+ifn b Sequence

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	1234567890					
AAGATCAACC	TCACCTACAG	GGCGGACTTC	AAGATCCCTA	TOGAGATGAC	GGAGAAGATG	1020
LysIleAsnL	euThrTyrAr	gAlaAspPhe	LysIleProM	etGluMetTh	rGluLysMet	
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CAGAAGAGIT	ACACTGCCTT	TOCCATCCAA	GAGATOCTCC	AGAATGTCTT	TCITGICITC	1080
	'yrThrAlaPh					_000
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AGAAACAATT	TCTCCAGCAC	TGGGTGGAAT	GAGACTATTG	TIGIACGICT	CTICCATICAA	1140
	heSerSerTh					1140
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CTCCACCAGC	AGACAGIGIT	TCTGAAGACA	GIACIAGAGG	AAAACCAAGA	CCAAACATTC	1200
LeuHisGlnG	lmThrValPh	eLeuLvsThr	ValleuGluG	lulvsGlnGl	uGluamieu	1200
					- Columbia	
ACCTCCCACA	TGICCICAAC	TGCTCTCCAC	TTGAAGAGCT	AUTROTOGACE	COMPANIES.	1260
ThrTrpGluM	l etSerSerTh	rAlaLeuHis	LeuLysSerT	vrTvrTmAr	of/alClnArr	1200
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TACCTTAAAC	TCATGAAGTA	CAACAGCTAC	CONTRIGRATICS	יבאניררונינות	אינוערמענענענע	1320
TyrLeuLysI	euMetLysTy	rAsnSerTvr	AlaTmMetV	alValAmal	aCluTlePhó	1320
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AGGAACTTTC	TCATCATTOG	AAGACTTTACC	ACADACTITIC	יוועבווייממממ	ጥልርልርን	1376
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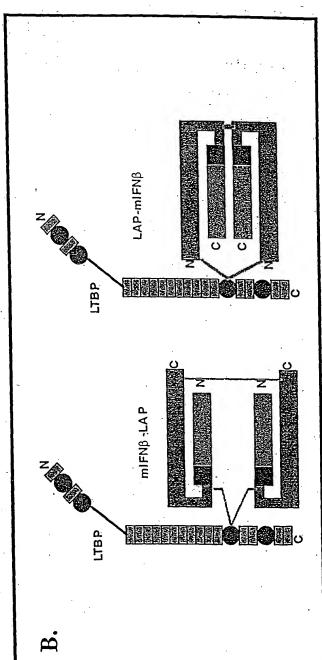
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ValValArgL e						300
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TyrTyrTrpA n						
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GIGGICOGAG C	AGAGATCTT	CAGGAACIT	CTCATCATI	C GAAGACTTAC	CAGAAACTIC	540
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CAAAACGAAT T	COGGGGAG	COCCATOCOC	G CICGGGCIT	r gggcgggag	GGGCTCXGCG	600
GlnAsnGluP h	eGlyGlyG	l yGlySerPro	o LeuGlyLeu	rpAlaGlyG	l yGlySerAla	
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AlaAlaLeuS e	rThrCysL	y sThrIleAs	p MetGluLeu'	V allysArgLi	y sArgIleGlu	
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GIGITOCICT O	CCCGCCAGA	<b>GCTGCGTCTG</b>	CTGAGGAGGC	TCAAGTTAAA	AGTIGGAGCAG	1020
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CACGIOGAGC TO	GIACCAGAA	ATACAGCAAC	AATTOCTGGC	CATACCTCAG	CAACCOGGCTG	1080
HisValGluL e	di Alenni A	siyrserAsn	AsnSerTrpA	rgTyrLeuSe	rAsnArgLeu	
CTGGCACCCA O	വാരണാഹ	ACACHOCONIA	m~~~~			
LeuAlaPmS e	TACOCOTOR T	ACTUMENT OF	TCTTTGATG	TCACCGAGI	TGTGCCGCAG	1140
LeuAlaProS e	DECCE	omunipized	Sernieaspv	arınırgıyva	ivalArgGin	
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AGCAGGGATA A	CACACTIGCA	AGTOGACATO	AACGCCTTCA	CTACCECCC	COGAGGTGAC	1260
SerArgAspA s	nihrleuGl	nValAspIle	AsnGlyPheT	hrThrGlyAr	qArqGlyAsp	1200
CICCCCACCA T	TCATGGCAT	GAACCCGCCT	TICCIGCTIC	TCATGGCCAC	CCCCCTCGAG	1320
LeuAlaThrI l	eHisGlyMe	tAsnArgPro	PheLeuLeuL	euMetAlaTh	rProLeuGlu	
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ArgAlaGlnH i	steuginse	rSerArg				

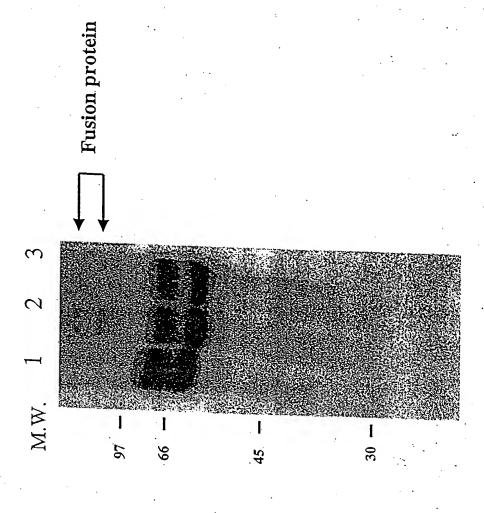
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60
                                                     40
 HU TGF-# 1
              MPPSGLRLLPLLLPLLULLV-LTPGPPAAGLSTCKTIOHELYKRKRIEAIRGOILSKLRLASPPSOGE-VP-PGP
 Hu TGE-8 2
              MHYCYLSAFLILH LYTVAL-----SLSTCSTLDMOOFHRKRIEAIRGQILSKLKLTSPP---EDYPEPEE
 Hu IGF-B 3
              MKHHLORALYVLALLNFATVSL-----SLSTCTTLDFGHIKKKRVEAIRGOILSKLRLTSPP---EPTV-MTH
 Ck TGF-B 4
 Fg 1GF-# 5
                                                100
                                                                        120
 Hu TGF-# 1
              LPEAVLALYNSTRORVAGESAEPE-PEP------EADYYAKEVIRVLHV----ETHHEIYDKFKQSTHSIYMFF
 HU TGF-B 2
              VPPEVISIYNSTROLL--OEKASR-RAAACERERSOEEYYAKEVYKIOMPPFFPS-ENAIPPTFYRPY-FRIVRF
 Hu TGF-# 3
              VPYQVLALYMSTRELL--EEHGER-KEEGCTOEHTESEYYAKEIHKFDMIQGLAE-HHELAVCPKGIT-SKVFRF
 Ck TGF-B 4
              -----GSPW-RPP-GTAPWSIG-SR--RA
 fg TGF-8 5
              PSEALF-LYMSTLE-VIREKATRE-EEEHVGHDOHIODYYAKOYYRF----ESITELEDHEFKFK------F
                  140
 Hu TGF-B 1
              HTSEL-----RE-AVPEPVLLS-RAELRLLRLKL----KV-EOHYELYQ-----KYSNHSWRYLSHRLLAPSDSPE
 Hu TGF-# 2
              DVSA------MEKNASNLV-KAEFRVFRLOHPK-ARVPEORIELYOILKSKOLTSPTORYIDSKVVKTRAEGE
 Ku TGF-8 3
              NYSS------YEKNRINLF-RAEFRYLRYPNPS-SKRNEGRIELFGILRP-DEHIAKGRYIGGKHLPTRGTAE
Ck TGF-B 4
              TASSSCSTSSRVRAEVGGRALLHRAELRHLROKAAADSAGTEORLELYOGYG-----NASHRYLHGRSVRATADDE
 fg TGF-8 5
              <u>MASHV-----RENYGMM-SLLH-HAELRMYK-KOTO--KNMOORHELFW--KYOEHGT</u>THSRYLESKYLTPVTODE
                  200
                                      220
             WLSFDVTGVVRQVLSRGGE1EGFRLSAHCSG ------DSRDHTLQVDIN-GFTTGR------RGDLAT1-----
 Hu TGF-B 1
 HU TGF-# 2
              WLSFDVTDAVHEWLHHKDRNLGFKISLHCPCCTFVPSHNYLIPNKSEELEARFA-GIDGISTYTSGOOKTIKSTRK
              WLSFDVTDTVREWLERRESNLGLEISIHCPCHTFOP-NGDILENIHEVMEIKFK-GVONEDDHGRGDLGREK---K
 HU TGF-# 3
             WLSFDVTDAVHOWLSGSELLGVFKLSVHCPCEHGPG-HADEHR1S1EGFEOQ------RGDHOS1A---K
 Ck TGF-B 4
             WHSFDYTKTVNEWLKRAEENEGFGLOPACKC ------PTPOAKD----IDTEGFPAL-RCDLASL--SSK
 fg TGF-8 5
                          260
                                                   1 580
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 HU TGF-# 1
              ----HGMNRPFLLLHATPLERA-OH--LQSS---RHRRALDTNYCFSST--EKNCCVROLYIDFRKDLGUKWIHEP
 Hu TGF-B 2
              KNSGKT---PHLLLHLLPSYRL-ESQ----QINRRKKRALDAAYCFRNY--ODNCCLRPLYIDFKRDLGUKWIHEP
 Hu TGF-B 3
              OKONH -- N-PHLILMMIPPHRL-DNPGOGGQ --- RKKRALDINYCFRHL -- EENCCVRPLYIDFRODLGWKWYHEP
 Ck TGF.B 4
              *KKRR**V*PYVLAMALPAERANE***LHSA***RRRROLDTDYCFGPGTDEKNCCVRPLY1DFRKDLOUKWIHEP
 Fg TGF-# 5
              ENT.....KPYL--MITSHPAERIDTVT SS---RKKRGYGGEYCFGNN--GPNCCVKPLYINFRKDLGNKVIHEP
                                                          360
 HU TGF-8 1
              KGYHANFCLGPCPYTWSLDTOYSKVLALYNOHNPGASAAPCCVPOALEPLPIVYYYGRKPKVEOLSHHIVRSCKCS
 Hu TGF-B 2
              KGYHANFCAGACPYLWSSDTOHSRYLSLYHTENPEASASPCCVSODLEPLTILYYTGKTPKTEOLSHHTVKSCKCS
 Ku TGF-# 3
              KGYYANFCSGPCPYLRSADTTHSTYLGLYNTENPEASASPCCVPODLEPLTILYYVGRTPKVEGLSHMVYKSCKCS
 Ck TGF-B 4
              KGYHANFCHGPCPYIWSADTOYIKYLALYNOHNPGASAAPCCVPOILDPLPIIYYVGRNYRVEOLSHHVVRACKCS
 fg TGF-B 5
              KGYEANYCLGNCPY1WSHDTQYSKVLSLYNONNPGAS1SPCCVPDVLEPLP11YYVGR1AKVEOLSHMVVRSCNCS
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Protein	- Sequence	Referenc
MMP-I/MMP-8	• •	
Human type I collagen (a1)	Ala-Pro-Gln-Gly775 ~ Ile776-Ala-Gly-Gln	80
Human type I collagen (α2)	Gly-Pro-Gln-Gly773~Leu776-Leu-Gly-Ala	80
Human type II collagen	Gly-Pro-Gln-Gly775~Leu776-Ala-Gly-Gln	80
Human type III collagen	Gly-Pro-Leu-Gly715~Ile716-Ala-Gly-Ile	80
Hūman αz-macroglobulin	Gly-Pro-Glu-Gly679~Leu680-Arg-Val-Gly	84
Rat α ₂ -macroglobulin	Ala-Ala-Tyr-Hison Leugar Val-Ser-Gln	84
Rat α _z -macroglobulin	Mct-Asp-Ala-Pheon ~ Leucoz-Glu-Ser-Ser	84
Rat \(\alpha_1\)-macroglobulin	Glu-Pro-Gin-Alassi ~ Leusst-Ala-Met-Ser	84
Rat a ₁ -macroglobulin	Gln-Ala-Leu-Ala685~Met686-Ser-Ala-Ile	84
Chicken ovostatin	Pro-Ser-Tyr-Phe ₆₇₃ ~Leu ₆₇₄ -Asn-Ala-Gly	.79
Human pregnancy zone protein	Tyr-Glu-Ala-Gly ₈₈₅ ~Leu ₆₈₆ -Gly-Val-Val	84
Human pregnancy zone protein	Ala-Gly-Leu-Gly687~Val.887-Val-Glu-Arg	84
Human pregnancy zone protein	Ala-Gly-Leu-Gly757~lle758-Ser-Ser-Thr	84
α ₁ -Protease inhibitor	Gly-Ala-Met-Phe ₃₅₂ ~Leu ₃₅₃ -Glu-Ala-Ile	85
Human aggrecan	lle-Pro-Glu-Asn ₃₄ ~ Phe ₃₄₇ Phe-Gly-Val	86
Human aggrecan	Thr-Glu-Gly-Glu ₃₇₃ ~Ala ₃₇₄ -Arg-Gly-Scr	86
Human cartilage link	Arg-Ala-Ile-His _{te} ~Ile ₁₇ -Gln-Ala-Glu	87
Human insulin-like growth factor	Leu-Arg-Ala-Tyr ₉₉ ~Leu ₁₀₀ -Leu-Pro-Ala	88
	ren-vik-vis- i Aidd _ reni00-ren-Lio-vis	. 99
binding protein-3	•	
MMP-2	Chatle How Cha a Lou Cha Challie	24
Guinea pig at(I) gelatin	Gly-Ala-Hyp-Gly ₃₄₇ ~Leu ₃₄₈ -Glx-Gly-His	24
Rat al(I) gelatin	Gly-Pro-Gln-Gly ₁₉₀ ~Val ₁₉₁ -Arg-Gly-Glu	30
Rat al(l) gelatin	Gly-Pro-Ala-Gly ₂₇₇ ~Val ₂₇₈ -Gln-Gly-Pro	30
Rat al(I) gelatin	Gly-Pro-Ser-Gly301~Leu302-Hyp-Gly-Pro	30 30
Rat \( a1(1) \) gelatin	Gly-Pro-Ala-Gly331~Glu332-Arg-Gly-Ser	
Rat al(I) gelatin	Gly-Ala-Lys-Gly ₃₆₁ ~Leu ₃₆₂ -Thr-Gly-Ser	30
Rat at (1) gelatin	Gly-Pro-Ala-Gly ₃₈₂ ~Gln ₃₈₃ -Asp-Gly-Pro	30
Rat \( \alpha \) (1) gelatin	Gly-Pro-Ala-Gly ₆₃₄ ~Phe ₆₃₅ -Ala-Gly-Pro	30 30
Rat al(I) gelatin	Gly-Pro-Ile-Gly ₆₇₆ ~Asn ₆₇₇ -Val-Gly-Ala	30 30
Rat al(I) gelatin	Gly-Pro-Hyl-Gly685~Ser686-Arg-Gly-Ala	22
Bovine type I collagen (a1)	Gly-Pro-Gln-Gly ₇₁₅ ~lle ₇₁₆ -Ala-Gly-Gln	22
Bovine type I collagen (α2)	Gly-Pro-Gln-Gly ₇₇₅ ~Leu-Gly-Ala	22 89
Human aggrecan	lle-Pro-Glu-Asn ₃₄₁ ~Phe ₃₄₂ Phe-Gly-Val	90
Human galectin-3	Pro-Pro-Gly-Ala ₆₂ ~Tyr ₆₁ -His-Gly-Ala	. 87
Human cartilage link	Arg-Ala-Ile-His16~Ile17GIn-Ala-Glu	. 87 87
Human cartilage link	Gly-Pro-His-Leu25~Leu26-Val-Glu-Ala	
Human insulin-like growth factor	Leu-Arg-Ala-Tyr, Leu, 200 Leu-Pro-Ala	88
binding protein-3	•	-
MMP-3		70
Human α ₂ -macroglobulin	Gly-Pro-Glu-Gly679~Leu680-Arg-Val-Gly	79
Human α ₂ -macroglobulin	Arg-Val-Gly-Phe684~Tyr685-Glu-Ser-Asp	79
Human α ₁ -antichymotrypsin	Leu-Leu-Ser-Ala360~Leu361-Val-Glu-Thr	91
α ₁ -protease inhibitor	Glu-Ala-Ile-Pro337 - Met358-Ser-Ile-Pro	91
Antithrombin III	ile-Ala-Gly-Argas,~Ser386-Leu-Asn-Pro	91
Chicken ovostatin	Leu-Asn-Ala-Gly677~Phe677-Thr-Ala-Ser	79, 92
Human aggrecan	Ile-Pro-Glu-Asn341~Phe342-Phe-Gly-Val	93
Substance P	Lys-Pro-Gln-Gln ₆ ~Phe-Phe-Gly-Leu	37
Human ProMMP-1	Asp-Val-Ala-Gln ₈₀ ~Phe ₈₁ -Val-Leu-Thr	43
Human ProMMP-3	Asp-Thr-Leu-Glues ~ Vales-Met-Arg-Lys	94
Human ProMMP-3	Asp-Val-Gly-His,2~Phe,1-Arg-Thr-Phe	- 94
Human ProMMP-8	Asp-Ser-Gly-Gly78~Phe79-Met-Leu-Thr	95
Human ProMMP-9	Arg-Val-Ala-Glu40~Met41-Arg-Gly-Glu	48
Human ProMMP-9	Asp-Leu-Gly-Argan~Pheaa-Gln-Thr-Phe	48
Human fibronectin	Pro-Phe-Ser-Pro689~Leu690-Val-Ala-Thr	. 21

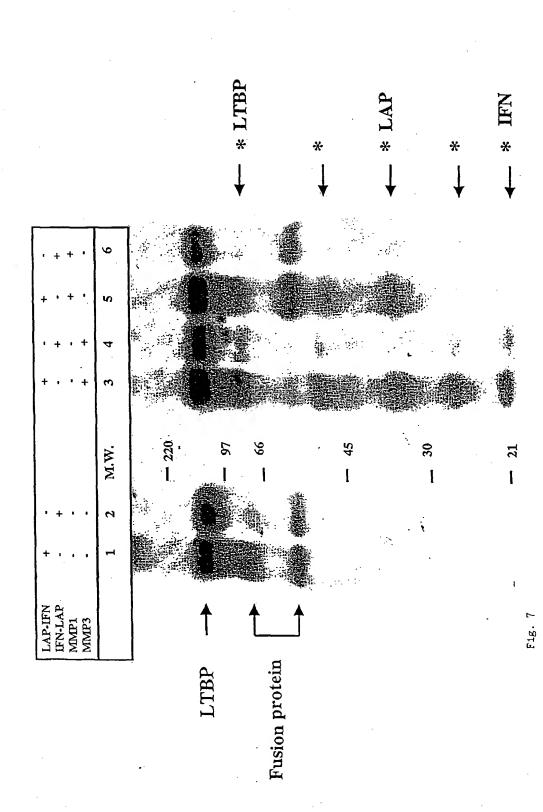
	Sequence	Referenc
Rutten insulin-like growth factor	Leu-Arg-Ala-Tyt ₉₀ ~Leu ₁₀₀ -Leu-Pro-Ala	88
binding protein-3	Ala-Pro-Gly-Asnion-Alairo-Ser-Glu-Ser	88
	Phe-Ser-Ser-Glu176~Ser177-Lys-Arg-Glu	88
Bovine a1(11) collagen. N-telopeptide	Ala-Gly-Gly-Ala115~Gln116-Met-Gly-Val	96
dovine al(II) collagen. N-telopeptide	Gln-Mct-Gly-Val 110~ Met 120-Gln-Gly-Pro	96
Bovine al(IX) collagen, NC2	Met-Ala-Ala-Ser~Leu-Lys-Arg-Pro	96
Bovine a2(IX) collagen, NC2	~Ala-Lys-Arg-Glu	96
Bovine a3(IX) collagen, NC2	~Leu-Arg-Lys-Pro	96
Bovine al(XI) collagen, N- telopeptide	Gin-Ala-Gin-Ala~ile-Leu-Gin-Gin	96
Human cartilage link	Arg-Ala-lle-His, ~lle, -Gln-Ala-Glu	87
Bovine insulin. B chain	Leu-Val-Glu-Alan ~ Leu, Tyr-Leu-Val	97
Bovine insulin, B chain	Glu-Ala-Leu-Tyr16~Leu17-Val-Cys-Gly	21,97
IMP-7	•	•
Human aggrecan	lle-Pro-Glu-Asn ₃₄ ~Phe ₃₂ Phe-Gly-Val	89
Human cartilage link	Gly-Pro-His-Leu25~Leu26-Val-Glu-Ala	87
Human prourokinase	Pro-Pro-Glu-Glu143~Leu144-Lys-Phe-Gln.	98
1MP-9	•	
Human type V collagen (α1)	Gly-Pro-Pro-Gly439~Val460-Val-Gly-Pro.	99
Human type V collagen (α2)	Gly-Pro-Pro-Gly445~Leu446-Arg-Gly-Glu	99
Human type XI collagen (α1)	Gly-Pro-Gly-Gly 439~ Val 440-Val-Gly-Pro	99
Human aggrecan	lle-Pro-Glu-Asn341~Phe342-Phe-Gly-Val	89
Human galectin-3	Pro-Pro-Gly-Ala62~Tyr63-His-Gly-Ala	90
Human cartilage link	Arg-Ala-lle-His16~Ilc17-Gln-Ala-Glu	87
1MP-10		
Human cartilage link	Arg-Ala-lle-His16~lle17-Gln-Ala-Glu	87
Human cartilage link	Gly-Pro-His-Leu25~Leu26-Val-Glu-Ala	87

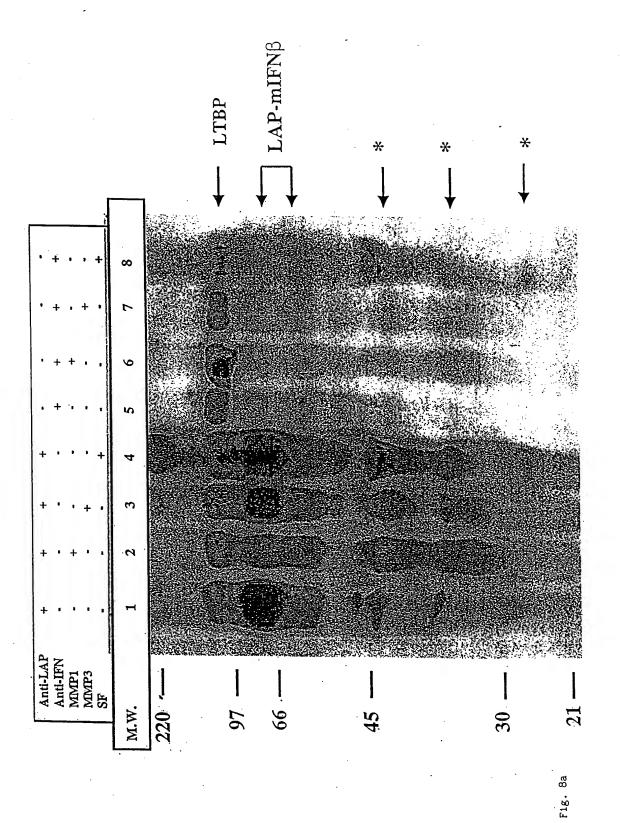


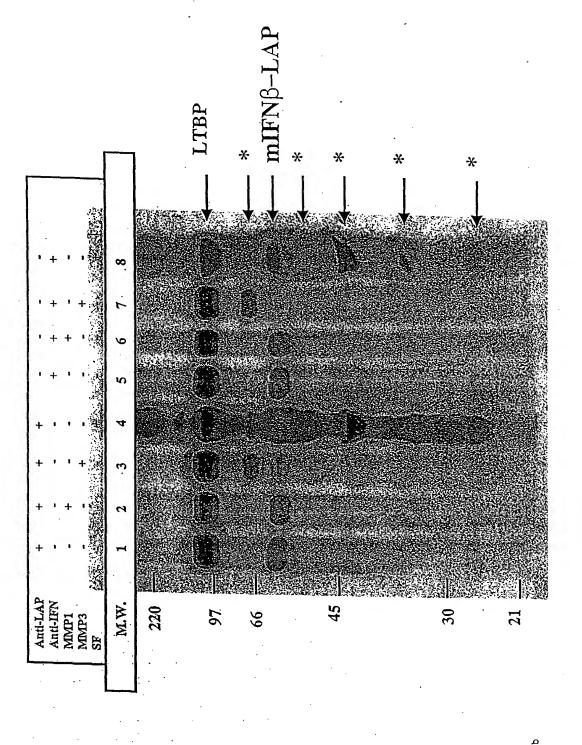
F1g. 5



F18. 6







F1g. 8b

Ξ.

2500

2000

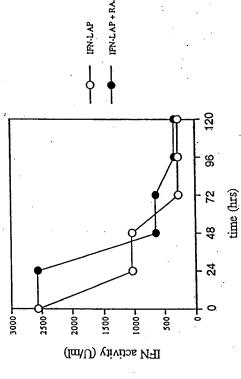
1500-

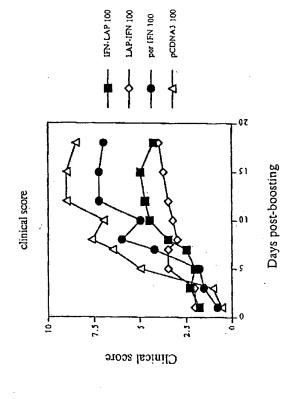
IFM activity (Units/ml)

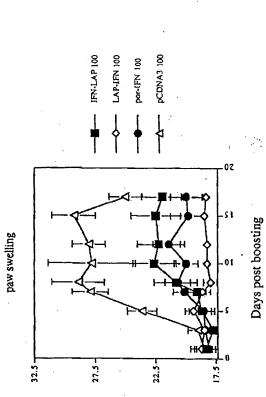
1000

3000









paw swelling (mmx $10^{-1}$ )